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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,331	12/18/2001	Andrew A. Young	030639.0031,UTL1	2765

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EXAMINER

LIU, SAMUEL W

ART UNIT	PAPER NUMBER
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1653

DATE MAILED: 07/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/889,331	YOUNG ET AL.	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-8 is/are pending in the application.
- 4a) Of the above claim(s) none is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-8 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____. | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Priority/Amendment

The preliminary amendment filed 2 January 2002 has been entered. Applicants' claim for the benefit of priority from U.S. provisional application, SN 60/116380, filed on 14 January 1999 is acknowledged. Claims 1-8 are pending and examined.

Drawing

The drawing (Figures 1-6 filed on 18 December 2001 acceptable subject to correction of the informalities indicated on the attached "Notice of Draftperson's Patent Drawing Review," PTO-948. In order to avoid abandonment of this application, correction is required in reply to the Office action. The correction will not be held in abeyance.

The following is the information on how to effect drawing changes.

1. New corrected drawings must be filed with the changes incorporated therein.

Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings MUST be filed within the THREE MONTH shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136(a) or for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948. All

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changes to the drawings, other than informalities noted by the Draftsperson, MUST be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings MUST be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

In addition, Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in abandonment of the application.

Specification/ Objections

The disclosure is objected to because of the following informalities:

(1) In Page 2, line 23, "GLP-1" should be spelled out in full at the first instance of use.

See also the terms "RP-HPLC" (Page 58, line 19); "IRMA" (Page 18, line 26); and "AUC")Page 18, line 34).

(2) In Page 65, 'the glutamic side chain' should be changed to "the glutamic acid side chain".

Correction is required

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7 and 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for conjugating PEG polymer to the claimed exendin peptides and use of the conjugated exendin peptides for suppressing glucagon secretion in human with type 2 diabetes and decreasing glucagon secretion during hyperglycemic clamps in a diabetes-related disorder in human, does not reasonably provide enablement for using the exendin conjugates to treat glucagonoma syndrome that is characterized by a necrolytic migratory erythematous rash, i.e. necrolytic migratory erythema (see Bloom, S. R. et al (1987) Am. J. Med. 82, (suppl 5B) 25-36). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant application is directed to a method of lowering plasma glucagon and treating disorders or diseases which are of characteristic of abnormally high blood glucagon levels in human by administering people a pharmaceutical composition comprising the PEG-conjugated exendin peptide. These disorders or diseases include glucagonoma and glucagonoma-related necrolytic migratory erythema. However, the specification does not provide working example, a description as to therapeutical background of the disorders, therapeutic dose and administering approach(es) applicable to the disorders.

The specification of the instant application only sets forth evidence regarding lowering plasma for treatment of hyperglucagonemia and type 2 diabetes (see example 4 and 5, respectively). The specification is silent as to therapeutic background of the relation of suppression of plasma glucagon to glucagonoma or glucagonoma-related necrolytic migratory erythema. Therefore, the skilled artisan cannot envision what is therapeutic relationship between

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glucagonoma or glucagonoma-related necrolytic migratory erythema and exendin biological activity. In light of these reasons stated above, adequate written description requires more than a mere statement that it is part of invention. The specification disclosure of the current application is insufficient to enable skilled artisan to practice the invention as broadly claimed without an undue amount of experimentation.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *in re* Wands 8 USPQ2d 1400, 1400 (Fed. Cir. 1998). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but not limited to: 1) the nature of the invention; 2) the breath of the claims; 3) the predictability or unpredictability of the art; 4) the amount of direction or guidance presented; 5) the presence or absence of working examples; 6) the quantity of experimentation necessary; 7) the relative skill of those skilled in the art.

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

(1) The nature of the invention/The scope of the claims:

Claim 1 sets forth a method of lowering plasma glucagon in a subject, comprising administering the modified exendin to a subject, and Claims 2 and 3 set forth that the said subject has glucagonoma-related necrolytic migratory erythema or glucagonoma, respectively.

As mentioned above, the claims as written are directed to use of the PEG conjugated exendin peptide as a pharmaceuticals to treat the glucagonoma and related disorder. The specification establishes the method of preparation exendin and PEG-conjugated exendin

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peptides, shows the peptide mediated decrease of plasma glucagon, and sets forth example for effect of the exendin peptide on glucagon secretion in people with type 2 diabetes. However, the specification is silent regarding a therapeutic relation of the exendin-mediated lowering glucagon secretion to glucagonoma and glucagonoma-related necrolytic migratory erythema which is necessary for the skilled artisan to practicing the invention, and does not provide working examples, guidance, teachings and supports (including medical and therapeutically background) for the claimed disorders. It appears that the disease states recited by the claims encompass any disorders or diseases required to lowering plasma glucagon levels which include glucagonoma and necrolytic migratory erythema. Also, the specification describes the preparation of the exendin conjugates and sets forth conjugation of one, or two or three PEG polymer(s) to the exendin peptide (see page 10, line 15-18). Claim 7, however, recites that one or more PEG polymers (without upper limit) can be linked to the exendin peptide; in consideration of Claim 8 that set forth the said one or more PEG molecules having molecular weight 500-20,000; hence, the combination number of such the result PEG-exendin conjugates as claimed is large and the exendin conjugates would be highly variant absent factual indicia to the contrary compared to the limitation set forth by the specification. Therefore, the scope of claims is broader (out of) the scopes of enablement.

(2) The state of the prior art:

The general knowledge and level of skilled in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Because, as mentioned in the foregoing statement, the combination number of the PEG-exendin conjugates (genus) as claimed is large and the conjugates are highly variant, and because each variant conjugate has

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different/distinct water-solubility (see page 10, lines 1-14) that determines pharmaceutical efficacy of the PEG-exendin applicable to the disorders or diseases absent factual indicia to the contrary, one of skilled artisan is require performing undue experimentation to screen, test for, and characterize each conjugate variant's solubility, biological stability (related to clearance by the kidney (see example 3) and pharmaceutical efficacy.

On the other hand, different disorders and diseases require different therapeutic procedures and protocols as well as doses and forms of pharmaceuticals. Even for treatment of a given disorder, parameters e.g. dose and administering time for achieving reasonable therapeutic effect of the exendin peptide is needed to be determined (see the bell curves of dose-dependent [figure 4(d)] and plasma concentration-dependent antidiabetic effect of the exendin [figure 4(f)], as well as time-dependent fashion [figure 4(b)], presented by Parkes, D. G. et al, Metabolism (2001) 50, 583-589). Since the above mentioned therapeutic parameters are also variant, the specification needs to provide sufficient guidance to support enabling.

(3) The quantity of experimentation necessary:

In the absence of working examples with regard to the above mentioned a unpredictable PEG-exendin conjugate variants and the undetermined therapeutic parameters referring to each variant, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention. Because of the reasons forgoing, the quantity of experimentation would be large and of unpredictability. The skilled artisan would be required to carry out a large body of search for water soluble, bio-stable PEG-exendin conjugate variant, and to conduct testing in suitable animal model and to determine suitable parameters for treatment of the disorders. For the

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instance, biological half-life of the antidiabetic composition needs to be determined prior to administering the composition; the clinical utility and development of the antidiabetic composition has been frustrated, at least in part, by its short half-life in man and the need for continuous or frequent administration (see figure 4(f), page 583 and 586, Parker et al). Because each therapeutic compound has different/distinct metabolic half-life, unpredictable result(s) would be associated with determination of the biological turn-over rate of the exendin peptide.

(4) The unpredictability of the art:

Because of the claimed method involves highly variant PEG-exendin conjugates, an uncertainty of outcome of administering the exendin-based pharmaceutical composition to a subject having glucagonoma syndrome and glucagonoma associated necrolytic migratory erythema, the invention is unpredictable in the absence of factual indicia to the contrary.

(5) The relative skill of those in the art:

The general knowledge and level of skill in the art do not supplement the omitted description with respect to an unpredictable number of the PEG-exendin conjugate variants. In view of the preceding factors (1-4), the level of skill in this art is high and requires at least a protein-engineer, an endocrinologist and a cell biologist at Ph.D. level with several years of experience in peptide chemistry as well as knowledge in peptide synthesis, endocrinology, oncology, and molecular biology; yet, even with a level of skill in the art as those mentioned in precedence, predictability of the results is still highly variable.

One of key parameters affecting the exendin therapeutic effect is the biological half-time *in vivo*. Drucker D. J. et al (Diabetes (1998) 47, 159-169) show that novel glucagon-like peptides i.e. exendin peptides are more potent than native glucagon-like peptide 1 (GLP-1) and

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higher biological stability of the exendin peptides than GLP-1 *in vivo* therapeutic application (see the left column of page 164 and the second paragraph, especially). This does not, however, necessarily reflect the exendin peptide or chemically modified exendin and strongly enough to resist to proteolysis during administration; as evidenced by Parkers et al, plasma concentration (stability) of exendin peptide is highly dependent upon time and mean of administering (see Figure 4(a) and 4(d)).

In light of the above-mentioned variant PEG-exendin conjugates, unpredictability of biological half-life of the conjugates when administered, pre-determination of several therapeutic parameters, e.g. dose, time, mean of administering, there is undue experimentation because of variability in prediction of outcome that is not addressed by the instant application disclosure, examples, teaching, and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and claims dependent are indefinite as to line 5 where “an an” is recited. Claim 1 is unclear as to whether or not a modified exendin is or is not an exendin agonist; whether or not a modified exendin agonist is or is not exendin agonist; and it is not clear as to what the modifications are compared.

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Claim 2 is indefinite as presented because it is not clear in the claim recitation per se, what the nexus of the treatment with a glucagon lowering amount of the compound has to the particularly recited disease/condition. Is the treatment supposed to affect the disease/condition state (if so, which way) or severity? See also Claim 3.

Claims 6 and 7 are in definite as to the recitation "...1-3 or 4" since the terminology should be "any one of ...".

Claim 7 is indefinite in the recitation "...is linked to one or more ..." as to (i) how many are polyethylene glycol (PEG) polymers are linked to the exendin molecule? (ii) which moiety of the exendin is linked to PEG polymer(s)? (iii) is it α -amine group of the N-terminus or side chain group of the exendin molecule linked to PEG polymer(s)? (iv) are multiple exendin peptides linked to a single PEG polymer? (v) Given the multiple exendin peptides are linked to multiple PEG polymers, whether or not the resultant conjugates are in network state, i.e. macro-biopolymer; if so, if it is water soluble?

Claim 8 is unclear as to the recitation "one or more"; how many PEG polymers are conjugated to the exendin molecule? Whether or not is the numbers of PEG-exendin conjugates unlimited?

Claim Rejections - 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

The claims 1, 4 and 6 are rejected under 35 U.S.C. 102(e) as being anticipated by Fine, S. A. et al. (US Patent SM: 6376549).

Fine et al disclose a method of using exendin-4 and derivatives thereof. The Fine et al patent also teach that one function of the exendin peptide is to reduce glucagon secretion (into blood circulation) when included in formulations and administered as a therapeutic composition (see column 3, line 46 –53 and Claim 34).

Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

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the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 4-8 are rejected under 35 U.S.C. 103(a) as being obvious over Fine, S. A. et al. (US Patent NO: 6376549), Drucker, D. J. (US Patent NO: 6051557) taken with Beeley, N. et al. et al. (WO9830231) and Frank, D. et al (US Patent NO: 4179397).

Fine et al teach use of exendin-4 and derivatives thereof to reduce glucagon secretion (into blood circulation) when included in formulations and administered as a therapeutic composition (see especially column 3, lines 46-53) in order for treating high-plasma-glucagon related disease e.g. diabetes, as applied to Claim 1.

Fine et al, however, do not teach conjugation of PEG polymer to exendin or exendin derivatives.

Drucker et al teach conjugate of PEG homopolymers to glucagon-related peptide (GLP), which is structurally and functionally related to exendin in order to enhance solubility of the peptide in aqueous solution, increase stability in storage, reduce immunogenicity, increase the peptide resistance to proteolytic degradation, and increase in vivo half life of the peptide (see column 19). Drucker et al teach covalent linkage of peptide hormone to one or more polymers; Of the polymers, PEG homopolymer is particularly preferred (see column 19, lines 26-28 and 44-45), as applied to the Claim 7 of the instant application having limitation that exendin peptide is linked to one or more PEG polymers.

Drucker et al do not teach the covalent conjugation of exendin to PEG polymers.

Beeley et al (WO 9820231), however, teach covalent modification of amino acid residues of exendin peptide, including Glycine N-modification, e.g. N-alkylglycine (see page 17 and 21) or tert-butylglycine (see page 22 and 24), and covalent conjugation of biopolymer(s) to the peptide terminus (C-terminus) (see formula II and pages 19-21), as applied to Claim 7 of the instant application. Beeley et al teach the exendin agonist is exendin-4 peptide (see page 11, line 19 and Claims 1, 17, 21 and 25), as applied to Claims 4-5 of the instant application. Beeley et al further teach that the pharmaceutical composition comprising the exendin peptide is administered to a human subject in a therapeutically effective amount (see Claim 27), as applied to Claim 1 and 6 of the instant application.

Frank, F. D. et al (US Patent SN: 4179337) teach that covalent linkage of polypeptides and peptide hormone e.g. insulin to polyethylene glycol (PEG) having a molecular weight of 500 to 20,000 daltons (see Claims 1 and 14-23 and columns 2-3), as applied to Claim 8 of the instant application. Note that the reference of Frank et al is cited by Drucker et al (US Patent SN: 6051557).

One of ordinary skill in the art would have combined the teachings of Fine et al, Drucker et al, Beeley et al and Frank et al for the following advantages: **(a)** exendin agonist that is a compound mimicking the biological effects of exendin (see page 9, line 9-12), which are virtually covalently modified exendin (see Formulas I and II at pages 16-23), offer better pharmaceutical activity than unmodified exendin peptide as taught by Beeley et al (compare Figure 4 [unmodified exendin] to Figure 5 [covalently modified exendin] at the same dose and time investigated); **(b)** the pharmaceutically formulated exendin-4 peptide, can be used with other

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pharmaceutics for therapeutic purpose (see column 3, lines 48-53), when used, augmentative effect by the exendin peptide is anticipated to other pharmaceutics, e.g. anti-diabetic agents; (c) PEG-GLP-2 conjugate (note that GLP-2 is functional analogue to intact exendin) has enhanced biological and chemical stability (i.e. increased *in vivo* $t_{1/2}$), better aqueous solubility, and less antigenicity and toxicity as taught by Drucker et al (see column 19); and (d) PEG having a MW 500-20,000 daltons offers a physiological active non-immunogenic water soluble polypeptide composition as demonstrated by Frank et al (see abstract and Claims 1 and 14-23, especially).

Given the above motivation one of ordinary skill in the art would have combined the teaching of Beeley et al as to preparation of bioactive exendin-4 analogs, the teaching of Drucker et al as to reward of using PEG-linked bioactive peptide (see the foregoing statement) and the teaching of Frank et al teaching as to molecular weight range of PEG for the conjugation, together with the teaching of Fine et al regarding the exendin as a pharmaceutics in regimen of therapy, or/and as a pharmacological enhancer to augment other pharmaceutics' effect on the disease(s) treatment as stated in the foregoing; which when combined, it would have result in pharmaceutically competent PEG-exendin compounds for lowering plasma glucagon and treating plasma glucagon-related disorders or diseases as claimed in the current application.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483.

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The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703 308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

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SWL

July 5, 2002

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